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Catalytic enantioselective conjugate addition of organometallic reagents

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Chapter 7

Asymmetric Catalysis with Phosphorus Amidites

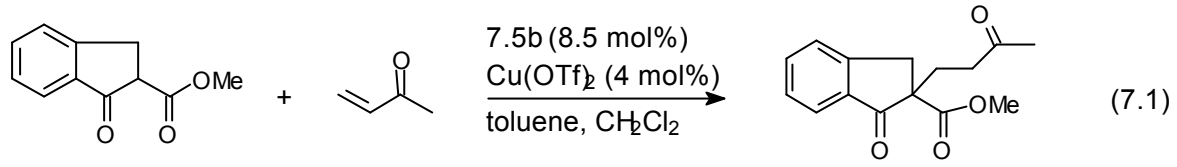
7.1 Introduction

In the previous Chapters we have seen that the enantioselective conjugate addition of dialkylzinc reagents to several enones is successfully catalysed by complexes derived from a copper salt and a chiral phosphorus amidite. Especially the observed ligand-acceleration in these copper mediated reactions, resulting in a fast and enantioselective conjugate addition, has stimulated us to examine this combination in other reactions. Therefore, catalysts derived in situ from copper salts (or in one case a rhodium salt) and chiral phosphorus amidites were used in preliminary experiments of other addition reactions (mainly carbon-carbon bond forming reactions). As already described in Section 1.2, there are several examples known of copper catalysed asymmetric carbon-carbon bond formations for a wide variety of substrates, furnishing products in high yields and with excellent enantioselectivities. Although these catalytic reactions are eligible candidates to examine, we have focussed our attention to addition reactions which lack highly enantioselective catalysts with a wide applicability.

7.2 Catalytic Michael addition reaction

The addition of methyl-1-oxo-2-indanecarboxylate to methyl vinyl ketone (MVK)
Carbon-carbon bond formation via Michael additions are most frequently performed under conditions of base catalysis, however, conjugate addition of 1,3-dicarbonyl compounds to enones can also be efficiently catalysed by metal complexes. All successful catalytic enantioselective examples are given in Section 2.6. Brunner and Hammer were the first to report significant enantioselectivity in a cobalt catalysed Michael addition of methyl-1-oxo-2-indanecarboxylate (7.1) to methyl vinyl ketone (MVK, 7.2, Eq. 7.1).[1] With (1S,2S)-(-)-1,2-diphenylethylene diamine as chiral ligand the Michael product 7.3 was formed with an enantioselectivity of 66%. Later on chiral copper complexes 7.4a-d were successfully applied in the same reaction with e.e.'s up to 70% (see Section 2.6).[2] Although the enantioselectivity strongly depends on the solvent (low e.e. in toluene, highest values in CCl_4) and the chiral catalyst (for example, with 7.4b an e.e. of 7% was found), this report prompted us to examine the combination of chiral phosphorus amidite 7.5b and $Cu(OTf)_2$ as catalyst in the reaction given in Eq. 7.1. With 4 mol% of $Cu(OTf)_2$ and 8.5 mol% of 7.5b the addition of 7.1 to 7.2 occurred

at ambient temperature in a solvent mixture of toluene and CH_2Cl_2 in almost quantitative yield (91%). In the literature reports[1,2] the e.e. values were based on the maximum optical rotation of Michael product 7.3.[3] However, control experiments by Keller in our research group revealed that these values are not in agreement with enantiomeric excesses determined by chiral HPLC analysis (Regis; (R,R)-Whelk-O 1 CSP).[4] Unfortunately, the e.e. determination of 7.3 by the latter method showed that no enantioselectivity was induced in the $Cu(OTf)_2$ / 7.5b catalysed Michael addition (e.e. < 5%).



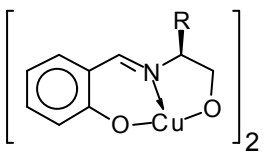
(7.1)

7.1 7.2 7.3

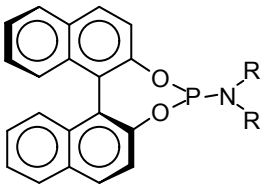
Compared to the enantioselective copper catalysed conjugate addition of dialkylzinc reagents to enones (Chapter 6) a stereogenic carbon center at a different position (at the Michael donor instead of the β-position of the enone) is formed in this reaction. Therefore, we have examined the Michael addition of dibenzyl malonate to cyclohexenone creating the stereogenic center at the β-position of the enone.

The addition of dibenzyl malonate to cylohexenone

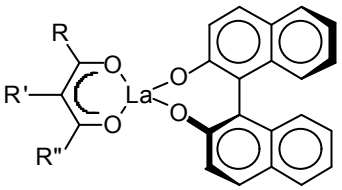
Recently, Shibasaki and co-workers reported a chiral lanthanum complex 7.6, which is highly effective as catalyst in enantioselective Michael additions of malonates to cyclic enones (yield > 90%, e.e. 75-95%).[5] The mode of addition in the preparation of the ester enolate 7.6 is crucial for this base catalysis (see also Section 2.6). When we examined the addition of dibenzyl malonate to cylohexenone in the presence of 4 mol% of $Cu(OTf)_2$ and 8.5 mol% of 7.5b we were disappointed that even after 15 days in toluene / THF at -15°C no trace of the Michael product was detected with TLC. Probably the presence of lantanum is essential for successful catalysis.



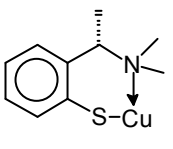
7.4a R = Et
7.4b R = Ph
7.4c R = $(CH_2)_3OH$
7.4d R = CH_2OH



7.5a R = Me
7.5b R = i-Pr



7.6

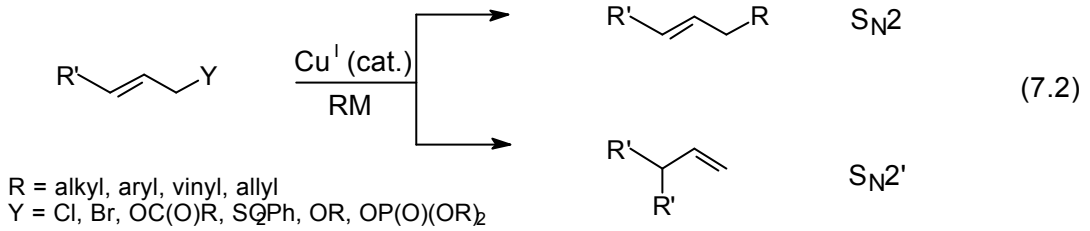


7.7

7.3 Copper catalysed S_N2' reaction

Introduction

The substitution reaction of organometallic reagents (RM = RMgX, R_2Zn, RZnX, etc.) with an allylic substrate promoted or catalysed by copper(I) salts or complexes is receiving increasing attention as a method for regio- and stereoselective carbon-carbon bond formation.[6] Depending on the reaction conditions used, the regioselectivity could be directed to afford either the product by S_N2 or S_N2' reaction (Eq. 7.2).

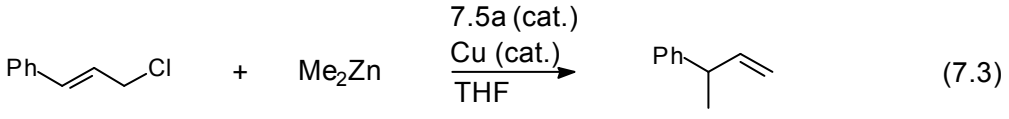


(7.2)

The creation of a new stereogenic center in the S_N2' reaction has led to highly diastereoselective reactions using a chiral allylic substrate,[7] but to our knowledge there is only one example known using achiral substrates and a chiral catalyst.[8] The S_N2' reaction of n-BuMgI with two allylic acetates [R'CH=CHCH$_2$OAc (R' = PhOCH$_2$- or cyclohexyl)] catalysed by the chiral arenethiolatocopper(I) complex 7.7 proceeded with an enantioselectivity up to 42%.[9]

The addition of dimethylzinc to cinnamyl chloride

Since it is known that organozinc reagents (RZnX and R_2Zn) does not react with allylic acetates in the presence of copper(I) complexes,[10] we have examined the copper catalysed addition of dimethylzinc to cinnamyl chloride (7.8) in the presence of chiral phosphorus amidite 7.5a (Eq. 7.3).[11] The S_N2' reaction catalysed by a mixture of CuCN (20 mol%), LiCl (20 mol%), and 7.5a (20 mol%) in THF as well as by $Cu(OTf)_2$ (10 mol%) / 7.5a (20 mol%) in THF proceeded smoothly furnishing the desired product 7.9 in good yield (ca. 80%).



7.8 7.9 (7.3)

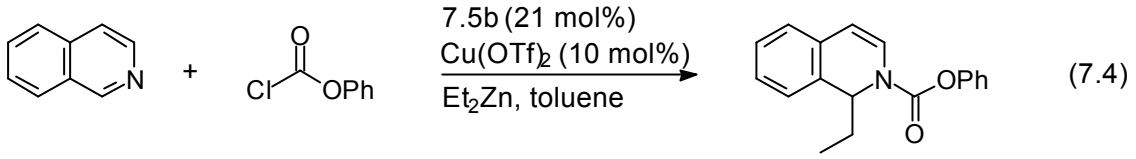
Unfortunately, the e.e. determination by chiral GC analysis (Lipodex C column) revealed no enantioselectivity for both cases. When the reactions were performed with diethylzinc instead of dimethylzinc the reaction given in Eq. 7.3 gave the corresponding product as well, however, the e.e. could not be determined using the method mentioned above (no separation of both enantiomers).
Probably the formation of a key-intermediate in which the allylic substrate anchors in a bidentate fashion [π-complexation of the C=C double bond to copper and coordination of the carbonyl-oxygen atom of the acetate function to M (for M, see Eq. 7.2)] to the chiral copper complex, as proposed in the literature,[9] is not possible with cinnamyl chloride resulting in a non-enantioselective reaction. It should be noted that allylic phosphates undergo S_N2' reaction with dialkylzinc reagents and this conversion deserves to be examined with our chiral catalytic system. Moreover, other combinations of organometallic reagent and substrates in the presence of copper / 7.5 are possibly more successful.

7.4 Catalytic asymmetric addition of organometallic reagents to imines

Introduction
Compared to the addition to carbonyl compounds, examples of asymmetric addition of carbon nucleophiles to imines have been reported scarcely. Two successful contributions have been emphasised in Section 1.2: the addition of organolithium reagents to N-arylimines (e.e.'s up to 91%) catalysed by a C_2-symmetric chiral bis(oxazoline) ligand[12] and an effective Strecker synthesis employing a chiral cyclic dipeptide as catalyst with exceptionally high e.e.'s (e.e.'s up to 99%).[13]
Imines are unreactive to diethylzinc even in the presence of stoichiometric amounts of amino alcohol promoters. Enantioselective alkylations with dialkylzinc reagents are reported to activated imines (N-diphenylphoshinoylimines, 'masked'-N-acylimines, and nitrones)[14] in the presence of (sub)stoichiometric amounts of chiral amino alcohols. Recently, the use of a catalytic amount of chiral auxiliary (L*MgBr, L* = (2S,3R)-4-dimethylamino-1,2-diphenyl-3-methyl-2-butoxide) was successful in the enantioselective addition of dialkylzinc reagents to nitrones (e.e. 56-78%), however, the presence of $Ph_3COMgBr$ (0.3 equivalent) is essential, probably to regenerate the chiral auxiliary.[15]

The addition of diethylzinc to 'activated' isoquinoline
In the research group of Prof. Kellogg the reaction of diethylzinc to isoquinoline (7.10) has been examined by Naasz.[16] In the presence of stoichiometric amounts of (chiral) amino alcohols no reaction occured between diethylzinc and isoquinoline either at

elevated temperatures or by activation with Lewis acids [BF_3, $Ti(Oi\text{-}Pr)_4$]. However, reaction of isoquinoline with phenyl chloroformate resulted in a activated iminium ion which was successfully treated with diethylzinc. Reactions at -70 °C in toluene gave the ethylated product 7.11, but with no enantioselectivity, even in the presence of stoichiometric amounts of several chiral amino alcohols.[16]



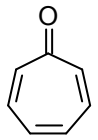
(7.4)

7.10 7.11

When we added a clear solution of $Cu(OTf)_2$ (10 mol%), phosphorus amidite 7.5b (21 mol%), and Et_2Zn (1 mmol) in 5 ml of toluene to a solution of isoquinoline and phenyl chloroformate in 10 ml of toluene at -50 °C, the ethylated product 7.11 was isolated after 16 h in 84% yield (Eq. 7.4). Unfortunately, the e.e. determination by chiral HPLC analysis (Daicel; Chiralpak AD) revealed no enantioselectivity. This lack of enantioselectivity is probably due to the high rate of the uncatalysed reaction under these reaction conditions (without chiral promoter the reaction proceeds at the same rate).[16] Less reactive substrates, for example nitrones, or even non-activated imines in the presence of a more reactive alkylating reagent seem to be feasible options for enantioselective additions to imines.

7.5 Addition of diethylzinc to tropone

2,4,6-Cycloheptatrien-1-one (tropone, 7.12) can be functionalised in a 1,8-fashion via the addition of nucleophiles such as enolates and Grignard reagents to give the corresponding 2-substituted dihydrotropone.[17] We were interested whether diethylzinc can be added (enantioselective) to tropone in a 1,8-fashion as well. Therefore, to a solution of $Cu(OTf)_2$ (3 mol%) and phosphorus amidite 7.5b (6 mol%) in toluene, tropone and Et_2Zn were added successively at ambient temperature (Eq. 7.5). The colour of the mixture changed from yellow to dark red and after 48 h the mixture was worked up (TLC revealed the disappearance of the starting material). However, a mixture of at least four products was obtained and we were not able to isolate one of them from this mixture. The low reactivity of diethylzinc (or the transmetalated reagent) seems to be the limiting factor for selective addition of diethylzinc to tropone.

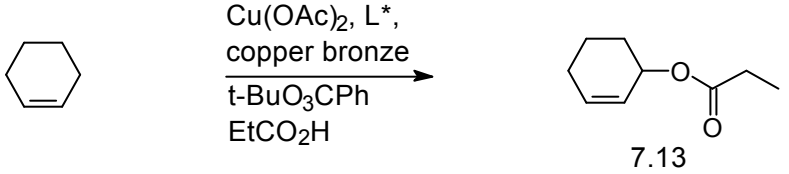


7.12

+ Et_2Zn $\xrightarrow{Cu(OTf)_2 / 7.5b}$ mixture of unidentified materials (7.5)

7.6 Copper catalysed enantioselective allylic oxidation

The functionalisation of alkenes and alkanes by catalytic enantioselective oxidations has been investigated to a wide extent.[18] Besides the highly enantioselective epoxidation of allylic alcohols[18a] and unfunctionalised alkenes,[18b] and the dihydroxylation of a wide range of alkenes,[18c] the asymmetric allylic oxidation is an interesting alternative for direct functionalisation of alkenes.[19] In our research group the copper catalysed (0.5 mol% $Cu(OAc)_2$ and 5 mol% copper bronze) allylic oxidation of 2-cyclohexene in the presence of propionic acid and peresters to yield the allylpropionate has been examined (Eq. 7.6). With (S)-proline as chiral ligand (L*, 3 mol%), 2-cyclohexenyl propionate (7.13) was obtained in ca. 60% yield (relative to the peresters) with e.e.'s up to 61%.[19]



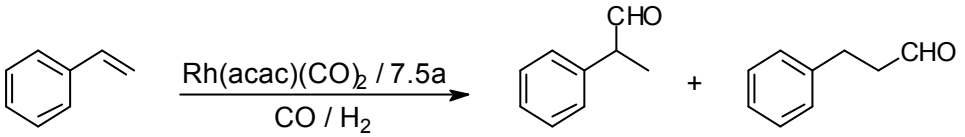
7.13 (7.6)

When this copper catalysed allylic oxidation was performed in the presence of phosphorus amidite 7.5a (3 mol%), the conversion to product 7.13 (70% relative to the oxidant) proceeded with a selectivity and at a rate comparable with the values found with (S)-proline as ligand.[19] An e.e. of 19% was determined by chiral GC analysis.[20] Both the conversion to the product and the observed enantioselectivity are an indication of a role of the chiral ligand in this catalytic oxidation. Investigations to optimise the conditions for this specific chiral ligand still has to be performed.

7.7 Rhodium catalysed enantioselective hydroformylation

The hydroformylation reaction of alkenes has enormous potential for the synthesis of optically active aldehydes and especially in the last three years significant advances

have been achieved using chiral ligands containing phosphorus donors.[21] Achiral phosphorus amidites have been applied as ligands in the rhodium catalysed hydroformylation of 1-octene and styrene.[22] In cooperation with the research group of Prof. van Leeuwen we have examined the chiral phosphorus amidite 7.5a as ligand in the rhodium catalysed hydroformylation of styrene (Eq. 7.7).[23]



7.14 7.15 (7.7)

The catalyst was formed with $Rh(acac)(CO)_2$ (0.1 mol%) and amidite 7.5a with 20 bar CO/H_2 at 50 °C in toluene for 2 h and successively treated with styrene under the same conditions. With a ligand to rhodium ratio of 10 the conversion after 4 h was 33% (branched/linear ratio of 7) which is comparable with the values observed for achiral phosphorus amidites.[22] Unfortunately, the e.e. determination of the corresponding alcohol of 7.14 by chiral GC revealed no enantioselectivity. With a ligand to rhodium ratio of 50 the catalyst is hardly active (4 % conversion after 4 h).
In practically all chiral catalysts for enantioselective hydroformylation reactions the ligands are bidentate phosphorus compounds, so probably better results will be obtained with a bidentate phosphorus amidite.

7.8 Concluding remarks

The preliminary experiments to develop other enantioselective addition reactions with a catalyst derived from a chiral phosphorus amidite revealed that these attempts have not been very successful. Only in the case of the allylic oxidation of 2-cyclohexene a good conversion to the product was accompanied with a significant enantioselectivity (19%). Although the product obtained via this reaction can be easily converted to interesting compounds, experiments to enhance the enantioselectivity seems to be indistinct.
In the Michael addition of the indanecarboxylate 7.1 to MVK the lack of enantioselectivity can probably be explained by the mechanism of the reaction. In this case the 1,3-dicarbonyl compound is activated by the copper complex prior to reaction furnishing a product with a stereogenic center at a different position (at Michael donor instead of enone) as compared with the products obtained with the conjugate addition

of dialkylzinc reagents to enones (described in the previous Chapters). Other ligands seems to be required for these reactions.
The addition of diethylzinc to allylic substrates, imines, and tropone described in this Chapter probably all proceed via the same organometallic reagent as proposed for the copper catalysed conjugate addition of dialkylzinc reagents to enones (Chapter 5 and 6). Unfortunately, with tropone or allylic acetate this alkyl-transferring reagent is not sufficiently reactive compared to the Grignard reagents, resulting in unwanted products or no addition reaction, respectively. The addition to allylic chloride 7.8 resulted in a S_N2' reaction with no enantioselectivity, probably due to the lack of a highly regulated transition state - bidentate anchoring of the substrate to the chiral copper complex seems to be required. The lack of enantioselectivity in the addition of diethylzinc to an activated imine (iminium ion) is probably due to competing uncatalysed addition. The search for the delicate balance between unreactive and slightly reactive substrates seems to be the determinant factor for this addition reaction.
Although the rhodium catalysed hydroformylation proceeded in the presence of 7.5a with a rate comparable as found for achiral phosphorus amidites, no enantioselectivity was observed. The use of bidentate phosphorus amidite ligands seem to be feasible options for this reaction.

7.9 Experimental section

All reactions in this Chapter were performed under argon using flame-dried standard Schlenk equipment, unless stated otherwise. For more general remarks, see Sections 3.8 and 6.8.

Materials
The following compounds were commercially available and used without purification: MVK (Aldrich), dibenzyl malonate (Aldrich), cinnamyl chloride (7.8; Aldrich), isoquinoline (7.10; Aldrich), phenyl chloroformate (Aldrich), tropone (7.12; Lancaster), 2-cyclohexene (Aldrich), $Cu(OAc)_2 \bullet H_2O$ (Aldrich), t-butylperoxy benzoate (Aldrich), and propionic acid (Aldrich).
Methyl-1-oxo-2-indanecarboxylate (7.1) was prepared by E. Keller according to a literature procedure.[24] For all other materials, see Sections 3.8, 5.6, and 6.8.

Addition of methyl-1-oxo-2-indanecarboxylate to MVK (preparation of 7.3)
To a cooled (-15 °C) solution of $Cu(OTf)_2$ (15 mg, 0.04 mmol) and 7.5b (36 mg, 0.085 mmol) in toluene (4 ml) and CH_2Cl_2 (5 ml) methyl-1-oxo-2-indanecarboxylate (0.19 g,

1.0 mmol) and MVK (190 mg, 2.7 mmol) were added. The mixture was stirred at ambient temperature for 3 days. The conversion of the indanone was confirmed by TLC analysis and the mixture was evaporated and purified by column chromatography (SiO_2, hexane:EtOAc 9:1) to afford the pure Michael product in 91% yield. The ^1H and ^{13}C NMR spectra were in agreement with those reported in the literature.[1,2] The e.e. was determined by HPLC analysis; Regis, (R,R)-Whelk-O 1 CSP, 20% EtOH in hexane, flow rate 1.0 ml/min (see also reference 4).

Addition of dimethylzinc to cinnamyl chloride (preparation of 7.9)
This procedure is typical for the S_N2' reactions described in this Chapter. To a cooled (-25°C) solution of $Cu(OTf)_2$ (36 mg, 0.10 mmol) and 7.5a (80 mg, 0.20 mmol) in THF (3 ml) Me_2Zn (1.0 ml, 2M in toluene, 2 mmol) was added. The resulting clear yellow solution was cooled to -60°C and cinnamyl chloride (0.16 g, 1.05 mmol) was added. The solution was stirred for 1 h at -60°C and 15 h at ambient temperature. The mixture was poured into 25 ml of aqueous 1 N HCl and extracted with diethyl ether (2 x 25 ml). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give the crude product 7.9. The ^1H and ^{13}C NMR spectra were in agreement with literature reports.[6,11] The e.e. was determined by chiral GC analysis (Lipodex C column).

Addition of diethylzinc to 'activated' isoquinoline (preparation of 7.11)
A preformed clear orange solution of $Cu(OTf)_2$ (36 mg, 0.10 mmol), 7.5b (88 mg, 0.21 mmol), and Et_2Zn (1.1 ml, 1.1M in toluene, 1.2 mmol) in toluene (5 ml) (prepared at -10°C and stirred for 15 min at ambient temperature) was added by syringe in 5 min to a cooled (-50°C) mixture of isoquinoline (118 µl, 1.0 mmol) and phenyl chloroformate (125 µl, 1.0 mmol) in toluene (10 ml). The mixture was stirred for 1 h at -50°C and 15 h at ambient temperature. The obtained clear solution was poured into 25 ml of aqueous saturated NH_4Cl and extracted with diethyl ether (2 x 25 ml). The combined organic layers were washed with aqueous 1 N NaOH (25 ml) and brine (25 ml), dried ($MgSO_4$), filtered, and evaporated to give the crude product. This material was purified by column chromatography (SiO_2, CH_2Cl_2:hexane 2:1) to afford pure 7.11 (yield 84%) as a white solid. ^1H and ^{13}C NMR were in agreement with those reported by R. Naasz.[16] The e.e. was determined by chiral HPLC analysis (Daicel; Chiralpak AD, 5.0% iPrOH in hexane, flow rate 0.5 ml/min).

Allylic oxidation of 2-cyclohexene (preparation of 7.13)
This experiment was performed by C. Zondervan, University of Groningen. Ligand 7.5a (0.12 g, 0.33 mmol), $Cu(OAc)_2 \bullet H_2O$ (9.0 mg, 0.05 mmol), and copper bronze (35 mg, 0.55 mmol) were suspended in acetonitrile (3 ml), 2-cyclohexene (3 ml), and propionic

acid under a nitrogen atmosphere. After stirring for 25 min at ambient temperature a green suspension was obtained and t-butylperoxy benzoate (1.0 ml, 5.0 mmol) was added. The mixture was stirred for 5 days at ambient temperature and poured into 25 ml of aqueous 2 N HCl and extracted with diethyl ether (2 x 25 ml). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (25 ml) and brine (25 ml), dried ($NaSO_4$), filtered, and evaporated to give the crude product 7.13. The conversion and e.e. were determined by chiral GC analysis (see text for data)

Rhodium catalysed hydroformylation of styrene
This experiment was performed by S. Deerenberg, University of Amsterdam. In an evacuated autoclave the catalyst was formed with $Rh(acac)(CO)_2$ (0.02 mmol) and amidite 7.5a (0.20 mmol) with 20 bar CO/H_2 at 50 °C in toluene (5 ml) for 2 h. The resulting mixture was treated with a solution of styrene (2.3 ml, 20 mmol) in toluene (6.7 ml) under the same conditions and after 4 h the conversion was determined by GC analysis (33%) (branched/linear ratio of 7). The aldehydes 7.14 and 7.15 were reduced to the corresponding alcohols, prior to e.e. determination (chiral GC analysis).

Acknowledgements
C. Zondervan, University of Groningen, and S. Deerenberg, University of Amsterdam are greatfully acknowledged for the performance of the allylic oxidation and the hydroformylation, respectively. E. Keller is thanked for the synthesis of compound 7.1 and for discussions concerning the Michael addition reactions and the addition reaction to tropone. Furthermore, H. van der Worp and R. Naasz are thanked for discussions concerning S_N2' reactions and diethylzinc additions to imines, respectively.

7.10 References and notes

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